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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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KNOBBE, MARTENS, OLSON & BEAR, LLP
2040 MAIN STREET
IRVINE, CA 92614

EXAMINER	
ROMEO, DAVID S	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 12/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/063,515	EATON ET AL.	
	Examiner	Art Unit	
	David S. Romeo	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 September 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *0906*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 09/29/2006 has been entered.

Maintained Formal Matters, Objections, and/or Rejections:

Claim Rejections - 35 USC §§ 101, 112

Claims 1–5 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

Applicants incorporate by reference their previously submitted arguments, and for the reasons of record assert that the specification contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented and therefore must be taken as sufficient to satisfy the utility requirement of 35 U.S.C. § 101. Applicants also submit that for reasons of record, the PTO has not met its burden of providing evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility; that even if the PTO has met its initial burden, Applicants' rebuttal evidence previously submitted and additional evidence submitted herewith is sufficient to prove that it is more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true; that as stated previously, Applicants' evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility; that even if the correlation between Applicants evidence and the asserted utility is not exact, such that there are exceptions to the correlation between the evidence and the asserted utility, this is sufficient to establish a utility; that exceptions between the evidence disclosed and the asserted utility is permissible - the standard is not absolute certainty. Applicants' arguments have been fully considered but they are not persuasive. The examiner incorporates by reference his previous response to applicants' previously submitted arguments. Neither the specification nor any of applicants' arguments or other evidence establish if the disclosed change in PRO874 mRNA expression is one of those cases where this is a correlation between a change in mRNA level and a corresponding change in the level of the encoded protein. Therefore, there is no reason for a skilled artisan to be

reasonably convinced that the PRO874 polypeptide will exhibit the asserted diagnostic behavior. In the absence of any testing of the expression of the PRO874 polypeptide, the specification does not provide some immediate benefit to the public for the PRO874 polypeptide.

Applicants point out that in other applications filed by Applicants that rely on data from the exact same disclosure, Example 18, and in which the Applicants have submitted substantially the same references in support of their asserted utility, the PTO has concluded that in Application Nos. 10/063,529, 10/063,530, 10/063,524, 10/063,582, and 10/063,583 the data presented in Example 18, which demonstrate differential expression of the nucleic acids encoding certain PRO polypeptides, also support a conclusion of differential expression of the PRO polypeptides, making the claimed PRO polypeptides and antibodies that bind the PRO polypeptides useful for diagnostic purposes. Applicants therefore request that the Examiner recognize the utility of the claimed invention, supported by the data presented in Example 18 and the numerous cited references, as was done in the other applications referenced above. Applicants' arguments have been fully considered but they are not persuasive. Suffice it to say that each case must be decided on its own merits based on the evidence of record.

Applicants submit that the gene expression data provided in Example 18 of the present application are sufficient to establish that the PRO874 gene is differentially expressed in lung tumor tissue as compared to normal lung tissue, and is therefore useful as a diagnostic tool for lung cancer; that this assertion is based on the results of RT-PCR analysis of pooled normal lung tissue and pooled lung tumor tissue using methods that are well-established in the art; that this utility is substantial, i.e. distinguishing tumor cells from normal cells is not an insubstantial or trivial utility without a real world use, and it is specific, i.e. it is directed to specific disease and is not a utility that the entire class of nucleic acids shares; that this asserted utility is credible, as one of skill in the art would readily believe that a nucleic acid sequence can be used as a marker to distinguish tumor tissue from normal tissue. Applicants remind the Examiner that Applicants enjoy a presumption that their assertions are true; that the Examiner must approach Applicants' assertion of utility as being sufficient to satisfy the utility requirement; that with respect to the use of the PRO874 nucleic acid to distinguish tumor from normal tissue, the Examiner must accept this assertion as true "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility;" that therefore, the question is whether the PTO has

established that there is a reason to doubt the objective truth of Applicants' assertion that using standard RT-PCR procedures to examine the expression of the PRO874 mRNA in pooled normal lung samples and pooled tumor lung samples, Applicants discovered that PRO874 mRNA is differentially expressed between normal and tumor such that it can be used as a diagnostic tool. Applicants' arguments have been fully considered but they are not persuasive. Applicants have not established anything regarding PRO874 expression because applicants have not tested PRO874 polypeptide expression.

Applicants argue that the PTO is arguing that because "high throughput technologies, such as DNA microarrays" produce differences in mRNA that are attributable to "disease-independent differences between samples," this establishes "a reason for one skilled in the art to question the objective truth" of Applicants' asserted utility which is based on RT-PCR analysis of pooled samples of normal and tumor tissue, not microarrays. Applicants respectfully submit that one of skill in the art would not accept that the PTO has established a basis to doubt Applicants' asserted utility. Applicants argue that those of skill in the art recognize that RT-PCR is a more accurate and reliable technique than microarrays (see, e.g., Kuo et al., (Proteomics 2005; 5(4):894-906), previously submitted); that therefore, it would be readily apparent to one skilled in the art that opinions regarding data from high-throughput techniques such as microarrays are simply not relevant to Applicants' RT-PCR data, and are not a reason to doubt the truth of Applicants' asserted utility; that thus, even if accurate, a point which Applicants do not concede, Hu's and LaBaer's opinions regarding microarray studies are not relevant to the utility of the instant application which does not rely on microarray data. Applicants emphasize that they are not asserting that microarray data are not reliable (that is apparently the PTO's position based on Hu and LaBaer), merely that Applicants are using a method that is recognized by those of skill in the art as more reliable and sensitive. Applicants argue that the PTO's argument misses the point of Applicants' reliance on Kuo; that Kuo is cited as evidence to support Applicants' assertion that Applicants' PCR data are more accurate and reliable than the microarray technique commented on by Hu and LaBaer; that Kuo supports this assertion because it is evidence that one of skill in the art would regard PCR as a more accurate and reliable method of assessing changes in mRNA; that thus, whether or not the microarray technique commented on by Hu and LaBaer yields "disease-independent" results is not relevant to Applicants' data because, as evidenced by

Kuo, PCR data such as Applicants' are more accurate and reliable than the microarray data relied on by Hu and LaBaer; that until the PTO provides evidence that transcript changes detected by PCR analysis of pooled normal and tumor samples are often "disease-independent," the PTO's rejection of the data in Example 18 based on Hu and LaBaer is misplaced, and Applicants' asserted utility must be presumed true. Applicants' arguments have been fully considered but they are not persuasive. From the evidence provided it cannot be ascertained whether Kuo's RT-PCR data was consistent or inconsistent with Kuo's microarray data. Therefore, Kuo does not provide a basis for applicants asserting that applicants' PCR data are more accurate and reliable than the microarray technique commented on by Hu and LaBaer. With respect to PRO874 mRNA expression, the fold difference in expression between tumor and normal is unknown and not reported. Hu and LaBaer caution researches from drawing conclusions based on small changes in the transcript expression. A gene whose change in expression is unrelated to the disease cannot be used as a marker for the disease no matter how accurately the change is measured.

Applicants also note that neither Hu nor LaBaer cite any references to support their assertions that "most [microarray differences] are attributable to disease-independent differences between the samples" and that "it is not always clear if [the microarray differences] are biologically meaningful." Applicants argue that in the absence of any supporting references, Applicants cannot independently evaluate these statements to determine what is meant by "disease-independent differences" and "biologically meaningful;" that read in light of the entire article and accompanying letter to the editor, Applicants assert that these statements should be interpreted to mean that the observed differences do not play a role in the development or progression of the disease state, or that such a role in the disease state has not yet been published; that a differentially expressed mRNA can serve as a marker of a disease even if it is "disease-independent" in the sense that it has no role in the cause or progression of a disease, or if any such role is not yet published in the literature. Applicants invite the PTO to provide support for an alternate interpretation of" disease-independent" as used in Hu and LaBaer. Applicants' arguments have been fully considered but they are not persuasive. The examiner declines to adopt applicants interpretation of "disease-independent differences" and "biologically

meaningful" because changes of mRNA or protein attributable to disease-independent differences between the samples are not dependent upon the disease.

Applicants' arguments that Hu and LaBaer are silent regarding the reliability of pooled samples are incorporated by reference. Applicants argue that the PTO presents no evidence to support these assertions; that thus, the PTO uses conclusory and unsupported arguments as the basis for dismissing the declaration of an expert; that as such, the PTO's position is inconsistent with the Utility Examination Guidelines which state, "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; that it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered" and also is inconsistent with the requirement of the PTO to support its assertions of fact; that absent supporting evidence, it is inappropriate for the PTO to dismiss Applicants' arguments and Mr. Grimaldi's opinion regarding pooled samples simply because the PTO wishes to take a contrarian position on the use of pooled samples in diagnostics. Applicants maintain that their expert has established that "[d]ata from pooled samples is more likely to be accurate than data obtained from a sample from a single individual." First Grimaldi Declaration at ¶5. Applicants argue that the Grimaldi declaration make clear that, in fact, "the results of the gene expression studies indicate that the genes of interest can be used to differentiate tumor from normal." First Grimaldi Declaration at ¶7. Applicants refrain from further rebutting the PTO's assertions because there presently are no facts on the record to support a position other than that of Mr. Grimaldi's. Applicants respectfully request that the PTO provide evidentiary support for its assertions regarding pooled samples in order to fully develop these issues under examination. Applicants' arguments have been fully considered but they are not persuasive. Pooled samples eliminate the effect of variation on applicants' conclusion regarding differential PRO874 mRNA expression. However, pooled samples do not eliminate the variation itself. Without knowledge of the degree of variation within the pool one would not know if any particular measurement from a tissue would indicate normal tissue or tumor tissue and would not know if tumor tissue could be distinguished from tumor tissue. The examiner believes that he has adequately supported his arguments.

Applicants argue that they do not know how to respond the PTO's statement that the first Grimaldi declaration is "in contrast with the specification's teachings," (see Office Action at 3),

since the Office has not explained how the declaration is in contrast with the quoted portion of the specification or what relevance any contrast between the two statements has to Applicants' asserted utility. Applicants' arguments have been fully considered but they are not persuasive. The first Grimaldi declaration states that the DNA libraries used in the gene expression studies were made from pooled samples of normal and of tumor tissues. The specification teaches that "one or more tumor tissues" were used (page 140, paragraph 0350).

Applicants argue that the Office's statement that "Hu and LaBaer are evidence that a skilled artisan would consider the precise level of PRO874 gene expression as relevant" is not supported by any reasoning or citation to Hu and LaBaer. Applicants' are unaware of any teaching in Hu and LaBaer regarding the need for a "precise level of PRO874 gene expression" to use it as a molecular marker to distinguish tumor tissue from normal tissue. Applicants argue that in fact, Hu and LaBaer teach nothing at all regarding developing diagnostic markers of cancer. In conclusion, Applicants submit that the evidence reported in Example 18, supported by the first Grimaldi Declaration, establish that there is at least a two-fold difference in PRO874 mRNA between lung tumor tissue as compared to normal lung tissue. Applicants argue that applicants' assertion that PRO874 mRNA can be used to distinguish lung tumor tissue from normal lung tissue must be presumed true by the Examiner unless there is a reason that one of skill in the art would doubt the objective truth of Applicants' statements; that Applicants have shown that the references by Hu and LaBaer are inapplicable to Applicants' RT-PCR data, and the PTO has provided no evidentiary basis for dismissing the Grimaldi Declaration; that thus, any challenge to the sufficiency of the data with respect to the utility of the nucleic acid is inappropriate; that therefore, the only issue which remains is whether the data in Example 18 regarding differential expression of the PRO874 mRNA are reasonably correlated with differential expression of the PRO874 polypeptide such that the claimed antibodies have utility as diagnostic tools as well; that even if the PTO has established a reasonable doubt regarding Applicants' assertion that they are reasonably correlated, Applicants' overwhelming rebuttal evidence is more than sufficient to establish that changes in mRNA level lead to corresponding changes in protein level. Applicants' arguments have been fully considered but they are not persuasive. Applicants previously argued that the "precise levels of gene expression are irrelevant" (Grimaldi declaration, Exhibit 1, 12/10/2004, paragraph 7). The examiner considers

Hu and LaBaer as evidence that a skilled artisan would consider the precise levels of gene expression as relevant.

Applicants argue that given Applicants' evidence of differential expression of the mRNA for the PRO874 polypeptide in lung tumors, it is likely that the PRO874 polypeptide is also differentially expressed; and proteins differentially expressed in certain tumors, and antibodies that bind such proteins, have utility as diagnostic tools. Applicants argue that the Examiner should approach these assertions of utility with a presumption that they are true. Applicants incorporate by reference the previous arguments that the Haynes, Gygi, Allman and Chen references are not relevant to the issue of whether differential mRNA expression levels for a particular gene lead to corresponding differential expression of the encoded protein, and will not repeat them here. In an attempt to illustrate why references which relate to static global levels of mRNA and protein across different genes are not relevant to Applicants' asserted utility, Applicants provide the following: Haynes and Gygi looked for a correlation between the level of mRNA and corresponding protein by plotting a single measurement of mRNA level vs. protein level for a large group of different genes. The only way that such a plot would result in a significant correlation is if there exists a global ratio between mRNA levels and protein levels common across all genes, i.e., that for every X copies of an mRNA, there are Y copies of the encoded protein, such that the ratio of X:Y is constant across all genes. The data of Haynes and Gygi indicated that the steady state ratio of mRNA:protein level varied for different genes, and hence no global ratio existed. Based on this, the references concluded that protein levels cannot be accurately calculated from mRNA levels, and that "it is evident that the analysis of mature protein products in cells is essential as there are numerous levels of control of protein synthesis, degradation, processing and modification." Haynes at 1863, right column, full paragraph 2. In contrast, applicants argue that applicants' asserted utility does not require knowledge of or even the existence of a global ratio between mRNA levels and protein levels; that nor do Applicants' assertions require calculation of protein levels based on measured mRNA levels; that unlike Haynes and Gygi, Applicants are not relying on a single measure of mRNA for a particular gene and then attempting to calculate protein levels based on a global ratio between mRNA and protein levels; that instead, Applicants are relying on differential mRNA expression, where mRNA levels are measured in two different conditions, i.e. tumor and normal. Applicants assert

that a change in mRNA expression level for a particular gene typically lead to a corresponding change in the expression level of the encoded protein; that the Haynes and Gygi references are applicable only to a completely unrelated issue - whether a single measure of mRNA levels can be used to predict protein levels - and therefore, none of the data or conclusions of these references have any bearing on Applicants' assertions. To exemplify the difference between the Haynes and Gygi references and Applicants' asserted utilities, Applicants offer an illustration and an analogy. Applicants argue that applicants are relying on a correlation between changes in mRNA level for a particular gene leading to a corresponding change in the level of the encoded protein when comparing tissues at two different times or conditions; that the PTO argues that because there is no correlation between levels of mRNA and protein across genes at a particular time one of skill in the art would not expect an increase or decrease in the amount of mRNA for a particular gene to result in a corresponding change in the amount of the encoded protein; that there does not need to be a global correlation across genes for there to be a correlation in changes for a particular gene; that this is analogous to a finding that on one gallon of gas, a hybrid car can travel 50 miles but a large truck can only travel 5 miles, or that to travel 50 miles, a hybrid car requires 1 gallon of gas, but a large truck requires 10 gallons; that there are many things which affect the fuel efficiency of an automobile; that based on these observations, one could conclude that given the lack of a global ratio of gas to miles, and the resulting lack of correlation between the amount of gas in an automobile and the distance it travels, one cannot predict how far an automobile will travel based on the amount of gas in the tank; that even if true, Haynes' data and conclusions are irrelevant to Applicants' assertion, which is that increasing or decreasing the amount of mRNA for a particular gene will result in a corresponding increase or decrease in the amount of the encoded protein; that this is analogous to increasing or decreasing the amount of gas in an automobile - it will travel farther if you add more gas, and not as far with less; that the fact that there are many things which affect fuel efficiency and therefore you cannot predict how far and automobile will travel without knowing if it is a hybrid or a large truck is irrelevant - both a hybrid and a truck travel farther on more gas, and not as far on less; that applicants emphasize, and that the PTO will recognize, that these are simplified illustrations to demonstrate the difference between the two issues being examined; that however, these illustrations make clear that even if there is no correlation in the first experiment looking at static levels of mRNA

and protein across genes, there can still be a correlation between changes in mRNA and protein for a particular gene as examined in the second experiment. Applicants' arguments have been fully considered but they are not persuasive. Applicants' are assuming a change in PRO874 polypeptide expression in two different cell samples without knowing the correlation between the change, if any, in PRO874 mRNA expression and the assumed change in PRO874 polypeptide expression. In the present case it is unknown what level of differences are being reported and if those differences are consistent and reproducible. Just as one could not predict the distances traveled on a gallon of gas in two different cars without knowing the mpg in each car, one could not predict a change in protein expression in two different cell samples without knowing that the change in mRNA is associated with a corresponding change in the level of protein. Maybe if you added two gallons of PRO874 mRNA gas to the tumor cell you might travel twice as many PRO874 polypeptide miles as compared to one gallon of PRO874 mRNA gas in the normal cell, all else being equal. However, the PRO874 polypeptide miles per gallon of PRO874 mRNA gas in either the tumor cells or the normal cells is unknown. According to the first and second Polakis declarations, your PRO polypeptide miles per gallon of gallon of PRO mRNA gas may vary in tumor cells and normal cells. The fact that a change in mRNA level for a particular gene may typically lead to a corresponding change in the encoded protein level does not tell a skilled artisan if, or how, PRO874 polypeptide expression changes because applicants have not provided any data regarding PRO874 polypeptide expression, because there are examples where such a correlation does not exist, because applicants have not established if the present case is one in which there is such a correlation, and because there are numerous levels of control of protein synthesis, degradation, processing and modification, which are only apparent by direct protein analysis.

Applicants argue that nowhere does Allman teach that a change in mRNA levels would not lead to a corresponding change in levels of the encoded polypeptide; that accordingly, Allman is not contrary to Applicants' asserted utility and does not support the PTO's position, and provides teachings consistent with Applicants' asserted utility; that applicants are not arguing that a change in polypeptide levels generally causes changes in mRNA levels or that polypeptide levels serve as indicators of mRNA levels; that this argument conflates cause and effect; that nor do Applicants argue that a change in mRNA levels is the sole cause of changes in the level of the

encoded polypeptide; that applicants merely submit that one skilled in the art would expect that a change in mRNA levels for a particular gene would generally lead to a corresponding change in levels of the encoded polypeptide; that Allman is consistent with Applicants' contentions because Allman teaches that for cells expressing higher levels of BCL-6 mRNA, BCL-6 polypeptide levels also were higher, relative to BCL-6 polypeptide levels in cells that expressed lower levels of BCL-6 mRNA; that accordingly, Allman does not support a rejection of the claims for lacking utility. Applicants' arguments have been fully considered but they are not persuasive. Unlike Allman, Applicants have not provided any testing of PRO874 polypeptide expression. To be consistent applicants must also accept the argument that no change in BCL-6 mRNA levels would lead to no change in the levels of BCL-6 protein, or that a change in BCL-6 protein expression would be associated with a change in BCL-6 mRNA expression. Allman demonstrates that this is not so. Therefore, Allman does not support applicant's position. The fact that a skilled artisan may expect a change in mRNA levels would generally lead to a corresponding change in the levels of the encoded polypeptide does not tell a skilled artisan if, or how, PRO874 polypeptide expression changes because applicants have not provided any data regarding PRO874 polypeptide expression, because there are examples where such a correlation does not exist, because applicants have not established if the present case is one in which there is such a correlation, and because there are numerous levels of control of protein synthesis, degradation, processing and modification, which are only apparent by direct protein analysis.

Applicants next address the PTO's reliance on Chen et al. Applicants argue that applicants addressed Chen's sentence bridging pages 311-312 because it is the same kind of irrelevant study of the global relationship between mRNA and protein conducted by Haynes and Gygi which the PTO continues to rely on; that in addition to pointing out why the global analysis conducted by Chen was not relevant, Applicants also addressed the remainder of Chen in their previous responses (Submission filed with Request for Continued Examination, mailed April 6, 2006, at 14-16) which Applicants incorporate by reference; that applicants have never asserted that a change in the level of mRNA is always associated with a change in protein levels; that instead, applicants are asserting that generally, differential expression of an mRNA (e.g. tumor vs. normal) leads to a corresponding differential expression of the encoded protein; that Figures 2. A-C of Chen support this assertion in that the authors conclude that for genes where a

statistically significant correlation was found, like those in the figure, this "suggests that a transcriptional mechanism likely underlies the abundance of these proteins in lung adenocarcinomas." Chen at 313, left column; that as for the other genes examined where no correlation was found, it remains unknown if there was any substantial change in mRNA levels. Applicants' arguments have been fully considered but they are not persuasive. Applicants' rely on the statement in Chen that "it is not possible to predict overall protein expression levels based on average mRNA abundance in lung cancer samples" (sentence bridging pages 311-312). However, this global analysis of the relationship between mRNA and protein abundance was in addition to and distinct from Chen's correlation a mRNA/ protein abundance in the tumor samples, and the examiner did not rely on this global analysis. According to applicants exhibits, arguments, declarations, and asserted dogma changes in the level of an mRNA are associated with a corresponding change in the level of the encoded polypeptide. Therefore, according to applicants' exhibits, arguments, declarations, and asserted dogma, a change in the level of an mRNA should be correlated with a corresponding change in the level of the encoded protein regardless of the type of sample. However, Chen states:

> "Correlation analyses showed that protein abundance is likely a reflection of the transcription for a subset of proteins, but translation and post-translational modifications also appear to influence the expression levels of many individual proteins in lung adenocarcinomas." Paragraph bridging pages 304 and 306.

Applicants have not tested PRO874 polypeptide expression. It is unknown if the reported change in PRO874 mRNA expression is associated with a corresponding change in PRO874 polypeptide expression.

Applicants argue that Applicants have not disparaged microarray data or proteomics data; that Applicants have merely stated that one of skill in the art would regard RT-PCR as more sensitive and reliable than microarrays, and therefore any opinions of Hu and LaBaer regarding the significance of microarray data are not applicable to Applicants' data based on RT-PCR; that it is the PTO's position which is inconsistent, as the PTO relies on Hu and LaBaer to claim that microarray data are unreliable, and at the same time relies on Chen et al., which uses microarray data to access changes in mRNA levels. Applicants' arguments have been fully considered but they are not persuasive. The examiner does not rely on Hu and LaBaer to assert that microarray

data are unreliable. It is applicants that have disparaged microarray data as lacking sensitivity, unreliable, and inaccurate.

Applicants note that the PTO has not explained how Hancock's statement that "the markers that are generated by proteomics are not always consistent with the markers that are generated from expression profiling" supports the PTO's assertion that "a skilled artisan would not know if, or how, PRO874 expression would change in tumors." Applicants argue that proteomics markers may not be consistent with expression profiling for a number of reasons; that in addition to the possibility that proteomics is not sufficiently developed to accurately assess the level of protein expression, it could also be that proteomics markers are not always consistent with expression profiling markers because molecules that change at the protein level are not changing at the mRNA level; that such an inconsistency between markers is not contrary to Applicants' assertion that changes in mRNA lead to changes in protein level; that applicants have not asserted that all protein changes reflect a change in mRNA level; that absent further explanation by Hancock as to why proteomics markers are not always consistent with expression profiling, Hancock is not inconsistent with Applicants' asserted utility, and therefore cannot support the PTO's rejection. Applicants' arguments have been fully considered but they are not persuasive. Hancock is evidence that a situation, such as the present one, wherein only a change in transcripts is presented, is a situation that would require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use for the polypeptide because applicants have not provided any testing of PRO874 polypeptide expression. The specification lacks a sufficient correlation between the test performed on PRO874 mRNA expression and the asserted utility of the claimed polypeptides.

Applicants submit a copy of a declaration by Randy Scott, Ph.D. (attached as Exhibit 1). Applicants also submit a copy of a second Declaration by Dr. Polakis (attached as Exhibit 2) that presents evidentiary data in Exhibit B. Applicants argue that Dr. Polakis has provided the facts to enable the PTO to draw independent conclusions. Applicants argue that the case law has clearly established that in considering affidavit evidence, the PTO must consider all of the evidence of record anew. Applicants also respectfully draw the PTO's attention to the Utility Examination Guidelines which state, "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to

disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered." Applicants' arguments have been fully considered but they are not persuasive. The second Polakis declaration has been considered. Like the first Polakis declaration, the second Polakis declaration does not provide any data concerning PRO874 mRNA expression, PRO874 polypeptide expression, or the correlation between the two in tumor tissue or normal tissue. The fact that there may be a commonly understood general rule or dogma that increased mRNA levels are predictive of corresponding increased levels of the encoded protein does not establish the correlation between the change, if any, in PRO874 transcripts and PRO874 polypeptide expression in tumors because there are examples of genes for which such a correlation does not exist, according to Dr. Polakis. The MPEP makes clear, "factual evidence is preferable to opinion testimony ... ." The MPEP also makes clear, "opinion" testimony is entitled to be considered, i.e., it is "admissible" in an ex parte proceeding. MPEP §716.01(c). The mere fact that opinion testimony is admissible (i.e., is entitled to be considered) does not per se mean it must be accorded controlling weight. In assessing the weight to be given expert testimony in an ex parte context, the examiner may properly consider, among other things:

(1) The nature of the fact sought to be established.

(2) The strength of any opposing evidence.

(3) The interest of the expert in the outcome of the case.

(4) The presence or absence of factual support for the expert's opinion.

Unless an "expert" states the underlying basis for an opinion, it may be difficult to accord the opinion significant weight. Opinions expressed without disclosing the underlying facts or data may be given little, or no, weight.

The facts to be established are whether or not the disclosed change in PRO874 transcripts is disease-dependent or disease-independent and whether or not there is a correlation between the reported change in PRO874 transcripts and a corresponding change in PRO874 polypeptides levels. The declarations do not provide any data concerning PRO874 mRNA expression, PRO874 polypeptide expression, or the correlation between the two in tumor tissue or normal tissue. According to the first Polakis declaration:

> The purpose of this research is to identify proteins that are abundantly expressed on certain tumor cells and that are either (i) not expressed, or (ii) expressed at lower levels, on corresponding normal cells. Paragraph 3.
>
> ... we have identified approximately 200 gene transcripts that are present in human tumor cells at significantly higher levels than in corresponding normal cells. Paragraph 4.

The corresponding paragraphs from the second Polakis declaration say essentially the same thing except that instead of stating "significantly higher levels than in corresponding normal cells" the second Polakis declaration at paragraph 4 states "significantly higher levels in normal human tissue." Both the first and second Polakis declarations indicate that the data was generated using microarray analysis, which applicants' have disparaged as inaccurate and unreliable. There is no evidence of record that either the PRO874 mRNA or the PRO874 polypeptide is abundantly expressed in either tumor tissue or normal tissue. Given the paucity of information regarding PRO874 mRNA expression in tumors and the evidence in the art that there are numerous levels of control of protein synthesis, degradation, processing and modification, which are only apparent by direct protein analysis, one skilled in the art would not know if the change in PRO874 mRNA expression was disease-dependent or disease-independent, would not know if or how PRO874 polypeptide expression would change in tumors, and would have a reasonable, legitimate basis to doubt the utility of the PRO874 polypeptide. Even if the examiner were to assume that the disclosed change in PRO874 transcripts could reasonably be correlated with an assumed change in PRO874 polypeptide expression, it still could not be ascertained if the assumed change in PRO874 polypeptide expression would be disease-dependent or disease-independent because it is unknown if the change in PRO874 transcripts is disease-dependent or disease-independent. Even if the examiner were to accept Dr. Polakis' conclusion, it still would be considered evidence that the skilled artisan would not know if or how PRO874 polypeptide expression would change in cancer because 20% of the cases examined do not show a correlation, according to first Polakis declaration, and 10% of the cases examined do not show a correlation, according to second Polakis declaration. The fact that there may be a commonly understood general rule or dogma that increased mRNA levels are predictive of corresponding increased levels of the encoded protein does not establish the correlation between the change, if any, in PRO874 transcripts and PRO874 polypeptide

expression in tumors because there are examples of genes for which such a correlation does not exist, according to the Polakis declarations.

The declaration under 37 CFR 1.132 filed by Randy Scott is insufficient to overcome the rejection of claims 1–5. Dr. Scott bases his conclusions on microarray data, which applicants have disparaged as lacking sensitivity, inaccurate and unreliable. Further, Dr. Scott does not provide any data concerning PRO874 mRNA expression, PRO874 polypeptide expression, or the correlation between the two in any type of tissue sample. The fact that there may be a commonly understood general rule or dogma that increased mRNA levels are predictive of corresponding increased levels of the encoded protein does not establish the correlation between the change, if any, in PRO874 transcripts and PRO874 polypeptide expression in tumors because there are examples of genes for which such a correlation does not exist, according to first and second Polakis declarations and because there are some exceptions on an individual gene basis, according to the Scott declaration. Neither the specification nor any of applicants' arguments or other evidence establish if the disclosed change in PRO874 mRNA expression is one of those cases where this is a correlation between a change in mRNA level and a corresponding change in the level of the encoded protein. Therefore, there is no reason for a skilled artisan to be reasonably convinced that the PRO874 polypeptide will exhibit the asserted diagnostic behavior. In the absence of any testing of the expression of the PRO874 polypeptide, the specification does not provide some immediate benefit to the public for the PRO874 polypeptide.

Applicants acknowledge that the correlation between changes in mRNA level and protein level is not exact, and there are exceptions. However, Applicants remind the PTO that the asserted utility does not have to be established to a statistical certainty, or beyond a reasonable doubt. Applicants argue that the fact that there are exceptions to the correlation between changes in mRNA and changes in protein does not provide a proper basis for rejecting Applicants' asserted utility. Applicants submit that considering the evidence as a whole, with the overwhelming majority of the evidence supporting Applicants' asserted utility, a person of skill in the art would conclude that Applicants' asserted utility is "more likely than not true." Applicants' arguments have been fully considered but they are not persuasive. Applicants are not being asked to establish the asserted utility to a statistical certainty, or beyond a reasonable doubt. Rather, the facts to be established are is the disclosed change in PRO874 transcripts is

disease-dependent or disease-independent and is there a correlation between the reported change in PRO874 transcripts and a corresponding change in PRO874 polypeptides levels. Applicants have not provided any testing of PRO874 polypeptide expression. The fact that there may be a commonly understood general rule or dogma that increased mRNA levels are predictive of corresponding increased levels of the encoded protein does not establish the correlation between the change, if any, in PRO874 transcripts and PRO874 polypeptide expression in tumors because there are examples of genes for which such a correlation does not exist, according to the Polakis declarations.

Applicants argue that the PTO takes the position that Applicants must present specific evidence directly demonstrating the utility of the claimed antibodies - specifically, direct evidence of differential expression of PRO874 polypeptide in tumor and normal tissue; that thus, the PTO implies the following argument: (1) the evidence of record demonstrates that there are exceptions to the general rule that increased mRNA levels correspond to increased levels of the encoded polypeptide; (2) because such exceptions exist, it is mandatory that specific data of differential PRO874 polypeptide expression in lung tumor tissue as compared to normal lung tissue be disclosed; and (3) since such is not disclosed, the claimed antibodies that bind the PRO874 polypeptide have no substantial utility; that adopting the PTO's standard for utility would result in a per se rule that a difference in mRNA expression cannot establish a utility for the encoded polypeptide and antibodies thereto; that thus, the PTO chooses to heighten the utility requirement to require specific, direct evidence of utility when there are exceptions to a generally accepted rule that is relied upon for utility. This heightened utility requirement is inconsistent with the Utility Guidelines and the courts; that there is no requirement that utility be dispositively proven; that furthermore, the applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt;" that nor is there requirement that only direct evidence of utility is sufficient to establish utility; that instead, it is established that indirect evidence that is reasonably indicative of utility is sufficient to fulfill the requirements of 35 U.S.C. §101; that furthermore, there is no requirement that indirect evidence necessarily and always prove actual utility; that instead, there only need be a reasonable correlation between the indirect evidence and the asserted utility; that the indirect evidence need not absolutely prove the asserted utility; that all that is required is that the tests be reasonably

indicative of the asserted utility; that in other words, there need only be a sufficient correlation between the indirect evidence and the utility so as to convince those skilled in the art, to a reasonable probability, that the novel compound will possess the asserted utility; that the PTO appears to consider the above guidance from the courts inapplicable to the present situation because in those cases the claimed compound had been tested, and, in the present test, the polypeptides to which the claimed antibodies specifically bind have not been tested; that however, the PTO's position fails to recognize the issue in question for the above cases; that the issue in question was whether or not Appellants' evidence (in vitro or animal testing of compound), which was different in nature from the asserted utility (therapeutic use of compound), was sufficient to fulfill the requirements of 35 U.S.C. §101 when there was a reasonable link between Appellants' evidence and the asserted utility; that in the present case, Applicants submit that their evidence (differential mRNA expression) is reasonably linked to the asserted utility (diagnostic use of the encoded polypeptide); that insofar as it is uncontested that differential mRNA expression is reasonably linked to differential polypeptide expression, Applicants submit that such linkage is sufficient to fulfill the requirements of 35 U.S.C. § 101 as provided by the guidance of the Utility Guidelines and the courts; that the PTO's heightened requirement for establishing utility of the presently claimed antibodies is contrary to the Utility Guidelines and the courts; that it is sufficient to present evidence of differential mRNA expression since it is understood in the art that differential mRNA expression is reasonably linked to differential polypeptide expression; that even if the PTO has presented evidence that changes in mRNA expression are not always correlated with changes in protein expression, Applicants' overwhelming rebuttal evidence is more than sufficient to establish that changes in mRNA level typically lead to corresponding changes in protein level; that as such, Applicants have established that it is more likely than not that one of skill in the art would believe that because the PRO874 mRNA is differentially expressed in lung tumor tissue as compared to normal lung tissue, the PRO874 polypeptide will likewise be differentially expressed in lung tumors; that accordingly, when the evidence is applied to the proper standard for utility, it is clear that this differential expression of the PRO874 polypeptide establishes the claimed antibodies useful as diagnostic tools for cancer, particularly lung cancer. Applicants' arguments have been fully considered but they are not persuasive. It is the examiner's position that

Applicants should provide substantial evidence of a diagnostic utility unless one of skill in art would accept such utility as obviously correct. There is no indication that a skilled artisan would accept without question that the reported change in PRO874 transcripts is tumor-dependent or that the PRO874 polypeptide is differentially expressed in tumor tissue as compared to normal tissue in a manner consistent with the reported change in PRO874 transcripts. Neither the specification nor any of Applicants' arguments, exhibits, declarations or other evidence provide any specific data disclosing if or how PRO874 polypeptide expression changes in tumor tissue. Instead, Applicants rely on a general correlation between mRNA expression and expression of the encoded protein rather than the specific correlation between PRO874 transcripts and PRO874 polypeptide expression to argue that it is more likely than not that a change in PRO874 transcripts is correlated with an assumed change in PRO874 polypeptide expression. Without any evidence of the expression of PRO874 in tumor tissue this argument is of no avail to Applicants. Applicants' arguments, exhibits and declarations only show that it is not implausible that invention will work for its intended purpose. In view of the countervailing evidence, Applicants' arguments, exhibits and declarations are insufficient to meet the utility requirement because they are insubstantial evidence that expression of the PRO874 polypeptide changes in a manner that corresponds to the reported change in PRO874 transcripts.

Applicants argue that specific utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention." Applicants submit that the evidence of differential expression of the PRO874 gene and polypeptide in lung cancer cells, along with the declarations and references discussed above, provide a specific utility for the claimed antibodies; that there are significant data which show that it is more likely than not that the PRO874 polypeptide is differentially expressed in lung tumor tissue as compared to normal lung tissue; that these data are strong evidence that the PRO874 polypeptide is associated with lung tumors; that thus, contrary to the assertions of the PTO, Applicants submit that they have provided evidence associating the PRO874 polypeptide with a specific disease; that the asserted utility as a diagnostic tool for cancer, particularly lung tumors, is a specific utility - it is not a general utility that would apply to the broad class of antibodies. Applicants' arguments have been fully considered but they are not persuasive.

Although the utility may be specific to the claimed invention, it is not substantial. Therefore, the claimed invention lacks a specific and substantial utility.

Claims 1–5 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

As Applicants recognize, a rejection under § 112, first paragraph, may be maintained on the same basis as a lack of utility rejection under § 101. A deficiency under 35 U.S.C. 101 also creates a deficiency under 35 U.S.C. 112, first paragraph. If the application fails as a matter of fact to satisfy 35 U.S.C. § 101, then the application also fails as a matter of law to enable one of ordinary skill in the art to use the invention under 35 U.S.C. § 112. Obviously, if a claimed invention does not have utility, the specification cannot enable one to use it. As such, a rejection properly imposed under 35 U.S.C. 101 should be accompanied with a rejection under 35 U.S.C. 112, first paragraph. The 35 U.S.C. 112, first paragraph, rejection set out a separate rejection that incorporates by reference the factual basis and conclusions set forth in the 35 U.S.C. 101 rejection. A 35 U.S.C. 112, first paragraph, rejection should be imposed or maintained when an appropriate basis exists for imposing a rejection under 35 U.S.C. 101.

Claims 1-5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants submit that looking at the sequence, it would be apparent to any skilled artisan that the first methionine in SEQ ID NO:10 is likely the start methionine, and that would be sufficient evidence to convey with "reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed." Applicants submit that the PTO has failed to meet its initial burden of "presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a

description of the invention defined by the claims." Applicants' arguments have been fully considered but they are not persuasive. The disclosure that it is conceivable and possible that other methionine residues located either upstream or downstream from the amino acid position 1 in the figures may be employed as the starting amino acid residue for the PRO polypeptides makes it clear that Applicants have not adequately described "amino acids 34-321 of SEQ ID NO: 10" because there is no evidence of record that amino acid #34 is employed as a start site. In the absence of any evidence that amino acid #34 is employed as a start site, the generic disclosure of what may be possible or conceivable does not convey with reasonable clarity to those skilled in the art that Applicants were in possession of the invention as now claimed.

Conclusion

No claims are allowable.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (571) 272-0890. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 9:00 A.M. TO 5:30 P.M. IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, BRENDA BRUMBACK, CAN BE REACHED ON (571) 272-0961.

IF SUBMITTING OFFICIAL CORRESPONDENCE BY FAX, APPLICANTS ARE ENCOURAGED TO SUBMIT OFFICIAL CORRESPONDENCE TO THE CENTRAL FAX NUMBER FOR OFFICIAL CORRESPONDENCE, WHICH IS (571) 273-8300.

CUSTOMERS ARE ALSO ADVISED TO USE CERTIFICATE OF FACSIMILE PROCEDURES WHEN SUBMITTING A REPLY TO A NON-FINAL OR FINAL OFFICE ACTION BY FACSIMILE (SEE 37 CFR 1.6 AND 1.8).

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING MAY BE OBTAINED FROM THE PATENT APPLICATION INFORMATION RETRIEVAL (PAIR) SYSTEM. STATUS INFORMATION FOR PUBLISHED APPLICATIONS MAY BE OBTAINED FROM EITHER PRIVATE PAIR OR PUBLIC PAIR. STATUS INFORMATION FOR UNPUBLISHED APPLICATIONS IS AVAILABLE THROUGH PRIVATE PAIR ONLY. FOR MORE INFORMATION ABOUT THE PAIR SYSTEM, SEE HTTP://PAIR-DIRECT.USPTO.GOV. CONTACT THE ELECTRONIC BUSINESS CENTER (EBC) AT 866-217-9197 (TOLL-FREE) FOR QUESTIONS ON ACCESS TO THE PRIVATE PAIR SYSTEM,

David Romeo

DAVID ROMEO
PRIMARY EXAMINER
ART UNIT 1647

DSR
NOVEMBER 28, 2006